11082090 BIOSIS NO.: 199799703235
Lipid lowering versus revascularization: An idea whose time (for testing) has come.
AUTHOR: Forrester James S(a); Shah Prediman K
AUTHOR ADDRESS: (a)Cedars-Sinai Med. Cent., 8700 Beverly Blvd., Rm. 5314 N. Tower, Los Angeles, CA 90048-1865**USA
JOURNAL: Circulation 96 (4):p1360-1362 1997
ISSN: 0009-7322
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: There is strong evidence that revascularization does not prevent myocardial infarction in patients with stable coronary artery disease (CAD). The anatomic basis for this counterintuitive conclusion seems to be that most myocardial infarctions occur at sites that did not previously exhibit an angiographically significant stenosis. These angiographic observations are further supported by thallium studies in stable CAD that demonstrate that the site of stress-induced ischemia is frequently not the site of subsequent myocardial infarction. Since both coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty are directed at more severe coronary stenoses, we are led to the remarkable conclusion that angiography does not identify, and consequently revascularization therapies do not treat, the lesions that lead to myocardial infarction. The pathology of coronary atherosclerosis provides the basis for understanding why revascularization does not prevent infarction: unstable lesions that cause infarction are not necessarily severely stenotic, and stenotic lesions are not necessarily unstable. In contrast to revascularization, lipid lowering reduces the rate of myocardial infarction by apprxeq 30% over a period of 5 years. Thus, we might postulate that lipid lowering is the more effective therapy for both prevention of acute myocardial infarction and long-term survival. The health policy and economic implications of this viewpoint, should it emerge in the management of coronary heart disease, are clearly substantial. Consequently, the relative roles of lipid-lowering therapy and revascularization, both alone and together, must now be determined. It is an idea whose time - for testing - has come.

Current Perspectives

# Lipid Lowering Versus Revascularization

## An Idea Whose Time (For Testing) Has Come*

James S. Forrester, MD; Prediman K. Shah, MD

*Abstract* There is strong evidence that revascularization does not prevent myocardial infarction in patients with stable coronary artery disease (CAD). The anatomic basis for this counterintuitive conclusion seems to be that most myocardial infarctions occur at sites that did not previously exhibit an angiographically significant stenosis. These angiographic observations are further supported by thallium studies in stable CAD that demonstrate that the site of stress-induced ischemia is frequently not the site of subsequent myocardial infarction. Since both coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty are directed at more severe coronary stenoses, we are led to the remarkable conclusion that angiography does not identify, and consequently revascularization therapies do not treat, the lesions that lead to myocardial infarction. The pathology of coronary atherosclerosis provides the basis for understanding why revascularization does not prevent infarction: unstable lesions that cause infarction are not necessarily severely stenotic, and stenotic lesions are not necessarily unstable. In contrast to revascularization, lipid lowering reduces the rate of myocardial infarction by ≈30% over a period of 5 years. Thus, we might postulate that lipid lowering is the more effective therapy for both prevention of acute myocardial infarction and long-term survival. The health policy and economic implications of this viewpoint, should it emerge in the management of coronary heart disease, are clearly substantial. Consequently, the relative roles of lipid-lowering therapy and revascularization, both alone and together, must now be determined. It is an idea whose time—for testing—has come. (*Circulation*. 1997;96:1360-1362.)

*Key Words* • myocardial infarction • lipids • angina • atherosclerosis

"Nothing is more sad," says Arthur Koestler, "than the death of an illusion." We believe that the illusion of cardiology is that bypass or dilatation of coronary stenoses reduces the risk of myocardial infarction. In this article, we will critically analyze the data supporting this view. We will then discuss the biological basis for the dissociation between the angiographic severity of a stenosis and its propensity to become a culprit lesion. Finally, we will speculate on the implications of confronting this illusion.

Strong evidence from the CABG literature indicates that revascularization does not prevent myocardial infarction.[1-4] For example, Muhlbaier et al[1] reported an observational 10-year follow-up of 5428 patients with medical and surgical therapy for CAD. In the cohort with ejection fraction >0.50, the incidence of nonfatal infarction was 49% for the surgically treated patients and 41% for the medically treated cohort. Smaller differences were found in other groups stratified by ejection fraction. The mortality rates, however, favored surgery. The authors speculated that although surgery does not reduce the likelihood of infarction, it may decrease the likelihood of a fatal infarction. This speculation is consistent with the prior report of Wiseman et al,[3] who compared the frequency of recurrent infarction in matched groups of 205 CAD patients treated either medically or surgically. At 5 years after discharge, the bypass patients had had more reinfarctions (40% versus 23%, $P=.007$), yet the cumulative mortality in the two groups was similar. Finally, in the CASS, the 3-year incidence of myocardial infarction in nonsurgical patients was 8%, whereas in the surgically treated group it was 10%.[5] Consistent with the other comparative studies, however, the mortality rate for those who developed infarction was lower in the surgically treated group. Taken together, these data support the conclusion that although surgery reduces long-term mortality in some subsets, it does not reduce the incidence of myocardial infarction in patients with stable CAD.

Although PTCA reduces the rate of acute reinfarction after thrombosis, there are fewer data for determining whether PTCA prevents myocardial infarction in stable CAD patients. Nishiyama et al[6] reported that the 5-year incidence of nonfatal myocardial infarction was not different between PTCA and medical therapy (2.5% versus 1.8%). Furthermore, meta-analysis of 3371 patients in eight randomized trials comparing CABG with PTCA suggests that the combined end point of cardiac death and nonfatal myocardial infarction is slightly higher in the PTCA group (risk ratio, 1.10).[7] From such data, we may speculate that in stable CAD patients, PTCA is unlikely to reduce infarction rate compared with medical therapy, since neither differs from CABG in this outcome measure. Aside from one small trial that is not sufficiently powered to analyze death and infarction,[8] there are no randomized trials of PTCA versus medical therapy. In the absence of such data, we may draw the conclusion that there are no data to support the

From Cedars-Sinai Medical Center, Los Angeles, Calif.
Correspondence to James S. Forrester, MD, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Room 5314 North Tower, Los Angeles, CA 90048-1865. E-mail forrester@csmc.edu

*In 1974, just before the thrombolytic era, Drs Eugene Braunwald and P.R. Maroko wrote a seminal editorial entitled "The Reduction of Infarct Size: An Idea Whose Time (For Testing) Has Come" (*Circulation*. 1974;50:206-209). The article influenced the thoughts of many young investigators of that era. We have chosen to paraphrase Braunwald and Maroko's provocative title.

**Selected Abbreviations and Acronyms**
CABG = coronary artery bypass graft surgery
CAD = coronary artery disease
CASS = Coronary Artery Surgery Study
PTCA = percutaneous transluminal coronary angioplasty

belief that revascularization reduces the rate of myocardial infarction.

The anatomic basis for this counterintuitive conclusion seems to be revealed by serial angiography. Most myocardial infarctions occur at sites that did not previously exhibit a significant stenosis. Moise et al[9] found that of 116 occluded coronary arteries at second angiography, 72% occurred in segments previously free of high-grade stenoses. A compilation of the published serial angiographic literature[10-14] suggests that only 13% of the culprit lesions have >75% stenoses before myocardial infarction. Finally, Kerensky et al [15] and Little et al[16] showed that in patients with stable CAD, infarcts in the month after CABG or PTCA often occur at untreated sites. After successful PTCA, 57% of the early infarctions occurred at a site that previously had an untreated, nonobstructive lesion.

The limitation of the serial angiographic data is that the culprit lesions are seldom imaged in close temporal proximity to the clinical event, so that rapid growth of a lesion just before myocardial infarction remains a possibility. By providing an image of the culprit lesion immediately after the event, postthrombolytic angiography has resolved this problem. For instance, Brown et al[17] found that the average percent diameter of coronary stenosis after thrombolysis was 56%. Thus, although angiographic evidence of coronary atherosclerosis establishes a major increase in the risk of myocardial infarction, it does not necessarily indicate the site at which coronary occlusion will occur.

Before analyzing the cause of this apparent paradox and its therapeutic implications, we must add some caveats of clarification. Angiographic studies have also shown that the more obstructive a plaque is, the more frequently it progresses to coronary occlusion.[18-21] In the CASS, for instance, the subsequent coronary occlusion rate was 2% for diameter stenoses of 5% to 49% and 24% for stenoses of 81% to 95%. On the other hand, because nonobstructive lesions are common and obstructive lesions are rare, the ratio of occlusions at sites with <50% diameter stenoses to those with >50% stenosis was 7.4 to 1 (2591 versus 347). Consequently, most myocardial infarctions evolve from mild to moderate stenoses. Since both CABG and PTCA are directed at more severe coronary stenoses, we are led to the remarkable conclusion that angiography does not identify, and consequently revascularization therapies do not treat, the lesions that lead to myocardial infarction.

The explanation for this second counterintuitive conclusion is found in the histology of plaques that cause myocardial infarction.[22] These plaques have four distinguishing characteristics: (1) a large extracellular lipid core, (2) a thin fibrous cap, (3) inflammation (many macrophages, few smooth muscle cells), and (4) eccentric distortion of the vessel lumen.[23,24] For instance, Davies et al[23] found that the lipid pool exceeded 40% of plaque volume in 91% of ruptured plaques, whereas only 10% of intact plaques had lipid pools of this size. Such plaques have been identified, by both pathology and angioscopy, as the culprit lesion in 75% to 95% of acute coronary syndromes.[25-27] This type of plaque, which is prone to disruption with subsequent formation of occlusive or subocclusive thrombus, need not be obstructive.

The mechanisms responsible for plaque destabilization and rupture of the lipid-rich plaque are both biochemical and physical. Oxidized LDL in the vessel wall stimulates expression of chemotactic factors for circulating monocytes, which enter the vessel wall. The monocytes are transformed into tissue macrophages by ingestion of LDL. Over time, the macrophages die, creating the extracellular lipid pool. After formation of a fibrous plaque over this necrotic core, activated macrophages at its margins express proteolytic enzymes that erode the fibrous cap. The lipid pool, semiliquid at body temperature, is vulnerable to physical distortion that increases the internal and external stress on the thinned fibrous cap, which, when it ruptures, can lead to formation of occlusive thrombus, causing acute myocardial infarction. Although these biochemical and physical factors are largely independent of percent diameter stenosis, the clinical impact of plaque rupture is not. Nonobstructive stenoses do not induce development of collateral vessels. For this reason, smaller plaques are more likely to cause a clinical event during thrombotic coronary occlusion because of the absence of protective collateral flow.[28] Thus, the pathology of coronary atherosclerosis provides the basis for understanding why revascularization does not prevent infarction. Plaque instability causes myocardial infarction. The unstable lesions that cause infarction are not necessarily severely stenotic, and stenotic lesions are not necessarily unstable.

This distinction between the instability of a plaque and its magnitude of stenosis extends to assessment of prognosis and selection of therapy. The long-established angiographic practice of quantifying the magnitude of focal stenoses and counting the number of diseased vessels does provide prognostic information about survival, at least in part because multivessel disease correlates with poor left ventricular function. When left ventricular function is normal, however, this approach is far less useful. Thus, an unanticipated outcome in the CASS Registry was that for medically treated patients with normal left ventricular function, the survival curves for nonstenotic CAD and severe three-vessel disease were indistinguishable.[5] In contrast, the level of blood lipids is a potent discriminator of long-term risk. Thus, Pekkanen et al[29] found that the 10-year risk of death in men with established CAD increased from 4% to 20% with an increase in the level of blood cholesterol from "desirable" (<210 mg/dL) to "high" (>245 mg/dL). These large differences in 10-year relative risk extend to asymptomatic men, although at a lower level of absolute risk (2% versus 5%). Recent large population studies from the United States, Finland, and Canada have confirmed these results.[30-32] The clinical trial correlate of these data is the ≈30% reduction in myocardial infarction over 5 years with lipid lowering.[33,34] On the basis of the observed progressive divergence of event rates between follow-up years 1 through 5 and the previously published data relating prognosis to cholesterol levels,

we may anticipate that the reduction in the rate of myocardial infarction will be substantially greater after 10 years of lipid-lowering therapy.

One might postulate that the most effective method for reducing the frequency of acute myocardial infarction in high-risk patients is lipid-lowering therapy rather than revascularization. The diverse lines of evidence that support this hypothesis include the limited effectiveness of revascularization for preventing myocardial infarction, the now-established causal role of plaque instability in acute infarction, and the recent randomized clinical trial results of lipid-lowering therapy that report long-term reduction in cardiac events. The health policy and economic implications of this viewpoint, should it be proven correct in the management of coronary heart disease, are clearly substantial. Unfortunately, the history of cardiovascular therapy has innumerable examples of ideas that were compellingly logical but wrong. Consequently, the relative roles of lipid-lowering therapy and revascularization, both alone and together, must now be determined. It is an idea whose time (for testing) has come.

## References


1. Muhlbaier L, Pryor D, Rankin J, Smith LR, Mark D, Jones R, Glower D, Harrell F Jr, Lee K, Califf R, Sabiston D Jr. Observational comparison of event-free survival with medical and surgical therapy in patients with coronary artery disease: 20 years of follow-up. *Circulation*. 1992;86(suppl II):II-198-II-204.
2. Davis KB, Alderman EL, Kosinski AS, Passamani E, Kennedy JW. Early mortality of acute myocardial infarction in patients with and without prior coronary revascularization surgery: a Coronary Artery Surgery Study Registry study. *Circulation*. 1992;85: 2100-2109.
3. Wiseman A, Waters D, Walling A, Pelletier G, Roy D, Theroux P. Long-term prognosis after myocardial infarction in patients with previous coronary artery bypass surgery. *J Am Coll Cardiol*. 1988; 12:873-880.
4. Mark D, Nelson C, Califf R, Harrell F, Lee K, Jones R, Fortin D, Stack R, Glower D, Smith L, DeLong E, Smith P, Reves J, Jollis J, Tceng J, Muhlbaier L, Lowe J, Phillips H, Pryor D. Continuing evolution of therapy for coronary artery disease: initial results from the era of coronary angioplasty. *Circulation*. 1994;89:2015-2025.
5. Mock ME. Survival of medically treated patients in the Coronary Artery Surgery (CASS) Registry. *Circulation*. 1982;66:562-568.
6. Nishiyama S, Iwase T, Ishiwata S, Komiyama N, Yanagishita Y, Nakanishi S, Seki A. Comparison of long-term efficacy of medical treatment versus percutaneous transluminal coronary angioplasty (PTCA) in single-vessel disease. *Jpn Heart J*. 1995;36:565-572.
7. Pocock S, Henderson R, Rickards A, Hampton J, King S, Hamm C, Puel J, Hueb W, Goy J, Rodriguez A. Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. *Lancet*. 1995;346:1184-1189.
8. Parisi A, Folland E, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. *N Engl J Med*. 1992;326:10-16.
9. Moise A, Clement B, Saltiel J. Clinical and angiographic correlates and prognostic significance of the coronary extent score. *Am J Cardiol*. 1988;61:1255-1259.
10. Ambrose J, Tannenbaum M, Alexopoulos D, Hjemdahl-Monsen C, Leavy J, Weiss M, Borrico S, Gorlin R, Fuster V. Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol*. 1988;12:56-62.
11. Little W, Downes T, Applegate R. The underlying coronary lesion in myocardial infarction: implications for coronary angiography. *Clin Cardiol*. 1991;14:868-874.
12. Ellis S, Alderman E, Cain K, Fisher L, Sanders W, Bourassa M, CASS Investigators. Prediction of risk of anterior myocardial infarction by lesion severity and measurement method of stenoses in the left anterior descending coronary distribution. *J Am Coll Cardiol*. 1988;11:908-916.
13. Hacket D, Verwilghen J, Davies G, Maseri A. Coronary stenoses before and after acute myocardial infarction. *Am J Cardiol*. 1989; 63:1517-1518.
14. Webster M, Chesebro J, Smith H, Frye R, Holmes D, Reeder G, Bresnahan D, Nishimura R, Clements I, Bardsley W, Grill D, Bailey K, Fuster V. Myocardial infarction and coronary artery occlusion: a prospective 5-year angiographic study. *J Am Coll Cardiol*. 1990;15:218A. Abstract.
15. Kerensky R, Kutcher M, Mumma M, Applegate R, Little W. Myocardial infarction late after successful PTCA: progression of disease versus reoccurrence. *J Am Coll Cardiol*. 1991;17:304a. Abstract.
16. Little W, Gwinn N, Burrows M, Kutcher M, Kahl F, Applegate R. Cause of acute myocardial infarction late after successful coronary artery bypass graft. *Am J Cardiol*. 1990;65:808-810.
17. Brown BG, Gallery C, Badger R, Kennedy JW, Mather D, Bolson E, Dodge H. Incomplete lysis of thrombus in the moderate underlying atherosclerotic lesion during intracoronary infusions of streptokinase for acute myocardial infarction: quantitative angiographic observations. *Circulation*. 1986;73:653-661.
18. Alderman E, Corley S, Fisher L, Chaitman B, Faxon D, Foster E, Killip T, Sosa J, Bourassa M, CASS participating investigators and staff. Five-year angiographic follow-up of factors associated with progression of coronary artery disease in the Coronary Artery Surgery Study (CASS). *J Am Coll Cardiol*. 1993;22:1141-1154.
19. Nobuyoshi M, Tanaka M, Nosaka H, Kimura T, Yokoi H, Hamasaki N, Kim K, Shindo T, Kimura K. Progression of coronary atherosclerosis: is coronary spasm related to progression? *J Am Coll Cardiol*. 1991;18:904-910.
20. Giroud D, Li J, Urban P, Meier B, Rutishauser W. Relation of the site of acute myocardial infarction to the most severe coronary arterial stenosis at prior angiography. *Am J Cardiol*. 1992;69: 729-732.
21. Waters D. Plaque stabilization: a mechanism for the beneficial effect of lipid-lowering therapies in angiography studies. *Prog Cardiovasc Dis*. 1994;37:107-120.
22. Falk E, Shah P, Fuster V. Coronary plaque disruption. *Circulation*. 1995;92:657-671.
23. Davies M, Richardson P, Woolf N, Katz D, Mann J. Risk of thrombosis in human atherosclerotic plaques: role of extracellular lipid, macrophage, and smooth muscle cell content. *Br Heart J*. 1993;69:377-381.
24. Gertz S, Roberts W. Hemodynamic shear force in rupture of coronary arterial atherosclerotic plaques. *Am J Cardiol*. 1990;66: 1368-1372.
25. van der Wal A, Becker A, van der Loos C, Das P. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. *Circulation*. 1994;89:36-44.
26. Forrester J, Litvack F, Grundfest W, Hickey A. A perspective of coronary disease seen through the arteries of living man. *Circulation*. 1987;75:505-513.
27. Mizuno K, Satomura K, Miyamoto A, Arakawa K, Shibuya T, Arai T, Kurita A, Nakamura H, Ambrose J. Angioscopic evaluation of coronary-artery thrombi in acute coronary syndromes. *N Engl J Med*. 1992;326:287-291.
28. Danchin N. Is myocardial revascularisation for tight coronary stenoses always necessary? *Lancet*. 1993;342:224-225.
29. Pekkanen J, Linn S, Heiss G, Suchindran C, Leon A, Rifkind B, Tyroler H. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. *N Engl J Med*. 1990;322:1700-1707.
30. Wong N, Wilson P, Kannel W. Serum cholesterol as a prognostic factor after myocardial infarction: the Framingham Study. *Ann Intern Med*. 1991;115:687-693.
31. Sigurdsson E, Sigfusson N, Agnarsson U, Sigvaldason H, Thorgeirsson G. Long-term prognosis of different forms of coronary heart disease: the Reykjavik Study. *Int J Epidemiol*. 1995; 24:58-68.
32. Connelly P, MacLean D, Horlick L, O'Connor B, Petrasovits A, Little J. Plasma lipids and lipoproteins and the prevalence of risk for coronary heart disease in Canadian adults. Canadian Heart Health Surveys Research Group. *Can Med Assoc J*. 1992;146: 1977-1987.
33. Anonymous. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-1389.
34. Shepherd J, Cobbe S, Ford I, Isles C, Lorimer A, MacFarlane P, McKillop J, Packard C. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333: 1301-1307.